PATENT

Attorney Docket No.: ST9401-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

re application of:

Laurent PRADIER *et al.*

Appl. No.: 08/716,209

Filed: October 9, 1996

For: RECOMBINANT ADENOVIRUS CODING FOR BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF)

Art Unit: 1647

Examiner: S. Gucker

Reply to Office Action

Commissioner for Patents
Washington DC 20231

REQUEST FOR EXTENSION OF TIME

Applicants request a three-month extension of time to respond to the Office Action mailed on November 23, 2001 (Paper No. 35). Accordingly, the time for response is extended up to and including May 23, 2002. A payment form covering the required extension of time fee is enclosed. In the event that any variance exists between the amount enclosed and the fees required by the U.S. Patent and Trademark Office, please charge or credit the variance to the undersigned's Deposit Account No. 50-1129. The Commissioner is hereby authorized to charge any fee required to keep this application pending and not accounted for, including the extension of time fee, to Deposit Account No. 50-1129.

05/24/2002 CNGUYEN 00000066 08716209
01 FC:117 920.00 OP

RESPONSE TO OFFICE ACTION

In response to the Office Action dated November 23, 2001 (Paper No. 35), applicants request reconsideration and timely notice of allowance. Each of the rejections, comments, and Requests for Information are addressed below.

I. Applicants' Claim to Priority

Applicants request clarification on the status of the PTO file and French priority document FR 94 03191. On the Office Action Summary Sheet, this document is listed as "not received." Applicants note that the PTO acknowledged receipt of the priority document from applicants or the IB in the Notification of Missing Requirements Under 35 U.S.C. § 371, dated November 25, 1996. The FR 94 03191 document was the only priority document at the time of filing. The PTO later notes (at page 5 of the Office Action, Paper No. 35) that the English translation of the priority document has not been received.

Applicants enclose herewith a certified copy of the French priority document FR 94 03191 and a certified translation of it into the English language. If additional documents are needed to perfect applicants' claim to priority, applicants would appreciation specific notification.

Applicants also note that the content of the French priority document and the present specification is, except for the Sequence Listing, essentially identical. In response to the PTO's comments at page 5 of Paper No. 35 (paragraph numbered 5), the claim to priority has now been perfected. Accordingly, applicants are entitled to rely on FR 94 03191 and its March 18, 1994 filing date.

The PTO specifically noted the non-functional E1 gene and the alleged lack of priority benefit to this subject matter (page 5 of Paper No. 35). At pages 9 and 10 of this application, the defective adenoviruses are described, in part. In a specific embodiment of the invention noted at page 10, applicants state, "the genome of the defective virus according to the invention comprises. . .the non-functional E1 gene and at least one non-functional E2, E4 or L1-L5 gene" (*see* page 10, lines 5-10). The same passage appears in the English translation of the French

priority document (*see* page 6, lines 11-14). This passage clearly indicates that "non-functional" genes of adenovirus can be a preferred aspect of the invention. Since the subject matter of the claims is sufficiently disclosed in the prior foreign application, benefit under 35 U.S.C. § 119(a) is appropriate. *Studiengesellschaft Kohle m.b.H. v. Shell Oil Co.*, 42 U.S.P.Q.2d 1674 (Fed. Cir. 1997).

II. The Provisional Rejection for Obviousness-type Double Patenting

Claims 27-28, 31-35, 37-38, 40-41, and 48-50 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting. As this is a provisional rejection, applicants' will address it when claims have been allowed in this or the copending application.

III. The Rejection Under 35 U.S.C. § 102(f)

Claims 27-28, 31-35, 37-38, 40-41, and 48-50 stand rejected under 35 U.S.C. § 102(f) because the applicants allegedly did not invent the invention. Applicants respectfully disagree.

The PTO apparently relies on the published PCT document WO 94/08026, which lists a different group of inventors, but with at least one inventor in common with this application. The WO 94/08026 document refers to an EPO application, which is the same EPO application applicants have amended the claim for priority to include in this case (Supplemental Reply of September 29, 1999).

Applicants respectfully point out that "an inventor may use the services, ideas, and aid of others in the process of perfecting his invention without losing his right to a patent." *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 225 U.S.P.Q. 634, 641 (Fed. Cir. 1985),

quoting Hobbs v. U.S., 171 U.S.P.Q. 713, 724 (5th Cir. 1971) (finding no error in inventorship, even though a component of the claimed invention was designed by a vendor). In accordance with this principle, an inventor may include material in his or her patent application that represents the "services, ideas, and aid of others" without changing the inventorship. The application can also include material and explanations about how a product can be modified to meet a particular requirement without changing the inventorship. *Hess v. Advanced Cardiovascular Systems, Inc.*, 41 U.S.P.Q.2d 1782 (Fed. Cir. 1997), *cert. denied* 117 S. Ct. 2459 (1997).

Applicants also respectfully point out that an applicant can claim priority benefit of an earlier foreign document that discloses the invention, even though the listed applicant(s) or inventor(s) of the foreign document differs from the U.S. application. The M.P.E.P. provides an example.

> Joint inventors A and B in a nonprovisional application filed in the United States Patent and Trademark Office may properly claim the benefit of an application filed in a foreign country by A and another application filed in a foreign country by B, i.e., A and B may each claim the benefit of their foreign filed applications. M.P.E.P. § 201.13.

As this example makes clear, there is no requirement for "identity of inventorship" between a U.S. application and a foreign priority document – one inventor in common can suffice for a proper claim to priority (*see* Paper No. 35, at pages 4-5).

The PTO notes the common claim to priority to an EPO document (EP92-402644) at page 4 of Paper No. 35. However, there are clear differences between the specification of this application and the WO 94/08026 document. Applicants respectfully submit that a common priority document cannot by itself lead to the alleged ambiguity of inventorship. Applicants also submit that if one compares the content of this application with that of the cited document (WO

94/08026), there is no ambiguity in the inventorship. Accordingly, there is no reason for the rejection under 35 U.S.C. § 102(f) and applicants respectfully request its withdrawal.

This application was filed with original claims directed to an adenovirus containing DNA encoding a BDNF, compositions containing the adenovirus, a cell infected with the adenovirus, and an implant comprising the cell. The claims also refer to adenovirus vectors where E1 and at least one of E2, E4, or L1-L5 genes are nonfunctional. The examples include adenovirus vectors with BDNF-encoding sequences, behavioral tests, performed *in vivo*, to demonstrate the use of these vectors, and the long-term and substantial expression of a BDNF shown in the data.

In contrast, the published claims of the WO 94/08026 document are directed to a recombinant DNA vector capable of directing (or "targeting" in claim 12) expression and/or transcription of a selected nucleotide sequence in the cells of the central nervous system. The claims also refer to adenoviruses with E1 and E3 deletions (see claim 3). The assays listed in the specification include references to neural cells, brain cells, and specific neurons. In addition to the marker gene for ß-gal expression, the genes for tyrosine hydroxlase, CNTF, and the a chain of hexosaminidase A are also listed.

One of skill in the art would have no difficulty identifying the differences between the specification of this application and the published WO 94/08026 document. The differences include the additional structures of the adenovirus vectors discussed, the research and experimental results for BDNF-encoding vectors, and the discussion of implants. From the *Shatterproof Glass* case, noted above, there is no reason why an inventor of the additional subject matter in this application could not both be an inventor in the earlier application and also include the "services, ideas, and aid" of one of the non-inventors. In addition, from the *Hess v. Advanced Cardiovascular* case noted above, an inventor in this case could modify a product of

the earlier application without affecting the inventorship in this case. And as the example from the M.P.E.P. noted above shows, there is no legal or logical reason why there must by identity of inventorship between an application and a foreign priority document.

Applicants respectfully request the withdrawal of this rejection.

IV. Response to Request for Information

At page 5 of Paper No. 35, the PTO makes a Request for Information ("Request") under 37 C.F.R. § 1.105.

Initially, applicants respectfully submit that the Request is unnecessary and improper in this case. The document the PTO cites as a basis for making the request is Science 259:988-990 (1993) (the "*Science*" document). As shown below, the information requested is available in printed publications and there is no apparent or reasonable basis to conclude that the printed publications are inaccurate or incomplete. Thus, the Request does not seek "reasonably necessary" information as required under 37 C.F.R. § 1.105. If 37 C.F.R. § 1.105 is being interpreted as a mechanism to request any information, applicants respectfully submit that the rule and/or its interpretation exceeds the Patent Office's authority or is contrary to the applicable laws defining proper administrative action.

The Request asks, among other things, whether or not the E1 gene and at least one of the E2, E4, or L1-L5 genes was non-functional in the AdRSVßgal vector discussed in the *Science* document. It also asks for an explanation of the construction of the adenovirus used in the *Science* document. This information is not reasonably necessary. The information sought is already present in the published documents discussed here, and perhaps elsewhere.

The *Science* document refers only to a Stratford-Perricaudet document for the AdRSVßgal vector used. For example, the first column of page 988 of the *Science* document lists reference (5) after introducing the vector AdRSVßgal for the first time. Each of the experiments detailed in the figures of the *Science* document refers to this same vector. When one reviews the Stratford-Perricaudet document (of record, *see especially* page 627), the AdRSVßgal vector is shown in a map and in a description of how it was constructed. "The recombinant virus is replication incompetent due to its deletion for the E1 genes." (Stratford-Perricaudet, *et. al.*, J. Clin. Invest. 90:626-630, column 1, page 627). It is apparent, then, that the replication incompetent nature of the AdRSVßgal vector is due to the deletion of the E1 genes. One of skill in the art, reading these two documents, could not reasonably conclude otherwise. Furthermore, the construction of the recombinant adenovirus is detailed in the Stratford-Perricaudet paper and applicants need not explain the same to the PTO.

Accordingly, applicants respectfully object to this Request for Information and request that it be withdrawn.

In order to provide a complete response and avoid abandonment of this application, applicants submit the following in response to the Request. A representative of the assignee asked a co-author of the *Science* document about the adenovirus used in the experiments reported in the *Science* document. A summary of the co-author's statements in response is that an E1 deleted adenovirus was used in the work reported in the *Science* document, which virus is now referred to as a "first generation" adenovirus. A first generation adenovirus is one with an E1 gene deletion. The first generation adenovirus does not, however, contain a deletion in the E2 region, for example.

Thus, the answer to the question or assertion in the Request that appears to ask whether or not the adenovirus of the *Science* document had a non-functional E1 gene and meets all other "claim limitations" (*see* Paper No. 35 at page 6) is that the adenovirus of the *Science* document contained a deletion in E1. This much was also shown in the Stratford-Perricaudet document. The adenovirus of the *Science* paper did not contain a BDNF encoding cDNA, or a deletion in the E2 gene, for example. Therefore, the adenovirus could not have included the other "claim limitations."

In the Request, the PTO also requires confirmation that or explanation of how the adenovirus in the *Science* document was made "replication defective" (*see* page 6 of Paper No. 35). As noted above and in the Stratford-Perricaudet document, the "first generation" adenoviruses are replication incompetent due to the lack of the E1 genes. For example, these adenoviruses must be grown in the 293 cell line, or the equivalent, to complement for the lacking E1 genes. The 293 cells contain part of the adenoviral genome encompassing the E1 region (*see* page 11, lines 14-18 of the specification). At the time the Stratford-Perricaudet and *Science* documents were first written, the "replication defective" aspect of these adenoviruses was likely associated with the nature of their recombinant genomes and the fact that complementing cell lines were required to produce them – thus they were considered replication incompetent. However, the first generation adenoviruses did not contain deletions in the E2 region, for example.

Applicants have provided a full and good faith reply to the Request. Further information on the adenovirus of the *Science* document is not readily available.

V. Rejections Under 35 U.S.C. § 103(a)

A. Barde in view of Le Gal La Salle (*Science* document)

Claims 27-28, 31-35, 37-38, 40-41, and 48-50 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Barde in view of Le Gal La Salle. Applicants respectfully disagree.

Applicants respectfully submit that, at best, the combination of Barde and Le Gal La Salle presents an "obvious to try" situation, which is not the standard for § 103. *See In re O' Farrell*, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988); and *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990). In fact, as repeated in the other § 103 rejections addressed below, the combination of Barde with each of the other references presents at best an obvious to try situation.

In this case, the Barde and Le Gal La Salle combination could not have predicted the long-term and substantial expression of a BDNF that the applicants have demonstrated. In addition, prior to applicants' invention, one skilled in the art could not have predicted the biological activity and therapeutic effects demonstrated by the expression of a BDNF in the brain of a mammal (*see* Examples 6-8, beginning at page 25 of the specification). Applicants submit that, in this case, the mere mention of a BDNF-encoding sequence and any adenovirus vector does not teach or suggest the claimed invention in a manner required under the law.

Furthermore, and contrary to the comments at page 7 of Paper No. 35, the necessary motivation to combine from the Barde document fails to suggest an adenovirus of the claimed invention. For example, the noted excerpt of Barde (col. 25, line 44 to col. 29, line 42) discusses cell lines or cultured cells to produce a BDNF protein product. It discusses BDNF, BDNF related substances, BDNF antagonists, and BDNF antibodies. It merely mentions that "it may be

possible to introduce cells actively producing BDNF" into areas of an animal in need of it (*see* col. 29, lines 38-42). Barde does not suggest, in a meaningful way that is significant to the appropriate standards for obviousness, a combination with a replication defective recombinant adenovirus.

In addition, as explained above, the Le Gal La Salle document does not discuss the E2, E4, or L1-L5 genes of adenovirus as the PTO asserts in this rejection (*see* page 6 of Paper No. 35). Accordingly, the combination of Barde and Le Gal La Salle does not teach or suggest the invention of claim 40.

For these reasons, applicants respectfully request the withdrawal of this rejection.

B. Barde in view of Wilson

Claims 27-28, 31-35, 37-38, 40-41, and 48-50 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Barde in view of Wilson. Applicants respectfully disagree.

Applicants incorporate the comments above concerning the deficiencies in the Barde document. The substitution of the Wilson document for Le Gal La Salle does not remedy the deficiencies. Again, at best, Wilson and Barde represent an obvious to try situation, which does not meet the standards for obviousness. Nothing in Wilson improves the ability of one of skill in the art to predict the long-term and substantial expression of a BDNF that the applicants have demonstrated.

Furthermore, the PTO has not shown how the Wilson document teaches or suggests the E2, E4, or L1-L5 genes of adenovirus. Accordingly, the combination of Barde and Wilson does not teach or suggest the invention of claim 40.

Applicants respectfully request the withdrawal of this rejection.

C. Barde in view of Levrero

Claims 27-28, 31-34, 37, 41, and 48-50 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Barde in view of Levrero. Applications respectfully disagree.

Applicants incorporate the comments above concerning the deficiencies in the Barde document. The substitution of the Levrero document for Le Gal La Salle does not remedy the deficiencies. Again, at best, Levrero and Barde represent an obvious to try situation, which does not meet the standards for obviousness. Nothing in Levrero improves the ability of one of skill in the art to predict the long-term and substantial expression of a BDNF that the applicants have demonstrated.

Furthermore, the PTO has not shown how the Levrero document teaches or suggests the E2, E4, or L1-L5 genes of adenovirus. Accordingly, the combination of Barde and Levrero does not teach or suggest the invention of claim 40.

Applicants respectfully request the withdrawal of this rejection.

D. Barde in view of Quantin

Applicants incorporate the comments above concerning the deficiencies in the Barde document. The substitution of the Quantin document for Le Gal La Salle does not remedy the deficiencies. Again, at best, Quantin and Barde represent an obvious to try situation, which does not meet the standards for obviousness. Nothing in Quantin improves the ability of one of skill in the art to predict the long-term and substantial expression of a BDNF that the applicants have demonstrated.

Furthermore, the PTO has not shown how the Quantin document teaches or suggests the E2, E4, or L1-L5 genes of adenovirus. Accordingly, the combination of Barde and Quantin does not teach or suggest the invention of claim 40.

Applicants respectfully request the withdrawal of this rejection.

E. Barde and Stratford-Perricaudet

Applicants incorporate the comments above concerning the deficiencies in the Barde document. The substitution of the Stratford-Perricaudet document for Le Gal La Salle does not remedy the deficiencies. Again, at best, Stratford-Perricaudet and Barde represent an obvious to try situation, which does not meet the standards for obviousness. Nothing in Stratford-Perricaudet improves the ability of one of skill in the art to predict the long-term and substantial expression of a BDNF that the applicants have demonstrated.

Furthermore, the PTO has not shown how the Stratford-Perricaudet document teaches or suggests the E2, E4, or L1-L5 genes of adenovirus. In fact, as discussed in the response to the Request for Information above, it is clear that the Stratford-Perricaudet document does not teach or suggest the manipulation of these adenoviral regions. Accordingly, the combination of Barde and Stratford-Perricaudet does not teach or suggest the invention of claim 40.

Applicants respectfully request the withdrawal of this rejection.

VI. Conclusion

Applicants believe that this application is now in condition for allowance. If the Examiner believes that prosecution might be furthered by discussing the application with

applicants' representative, in person or by telephone, we would welcome the opportunity to do so.

Applicants have provided for a three-month extension. No additional extension of time fees, requests for extension of time, petitions, or additional claim fees are believed to be necessary to enter and consider this paper. If, however, any petitions or extensions of time are required or any fees are due in order to enter or consider this paper or enter or consider any paper accompanying this paper, including fees for net addition of claims, applicants hereby request any extensions or petitions necessary and the Commissioner is hereby authorized to charge our Deposit Account #50-1129 for any fees.

Respectfully submitted,
WILEY REIN & FIELDING LLP

Date: May 23, 2002

By: _____
David J. Kulik Reg. No. 36,576

WILEY REIN & FIELDING LLP
Attn: Patent Administration
1776 K Street, N.W.
Washington, D.C. 20006
Telephone: 202.719-7000
Facsimile: 202.719-7049

Enclosures: Submission of Priority Document and Certified Translation into English
(Certified copy of FR 94 03191 and Certified English Translation)

WRFMAIN 1125870.1